

Applicant: B. Jack Longley
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REMARKS

Claims 50-57 are pending in the subject application. Applicant has amended the specification and claim 57. Accordingly, upon entry of this Amendment, claims 50-57 are still pending and under examination.

Applicant maintains that these amendments to the specification and claims do not raise any issue of new matter, and that these claims are fully supported by the specification as originally filed. Accordingly, applicant respectfully requests that this Amendment be entered.

In view of the arguments set forth below, applicant maintains that the Examiner's objections and rejections made in the December 4, 2003 Office Action have been overcome, and respectfully requests that the Examiner reconsider and withdraw same.

Claimed Invention

This invention provides methods for treating or preventing cutaneous inflammation. These methods comprise administering to a subject an amount of an antibody that binds to kit protein, thereby preventing or treating cutaneous inflammation.

This invention is based on the *surprising discovery* that inhibition of the kinase enzymatic reaction of kit protein *in vivo* with an anti-c-kit antibody, e.g., ACK2, can decrease cutaneous inflammation.

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Formalities

The Examiner objected to the specification since the preamble of the specification did not reflect the issued parent application. The Examiner also objected to Claim 57 since "administration" may be intended to be "administering".

Applicant has amended the specification and Claim 57 to fully address the Examiner's concerns.

Rejection Under 35 U.S.C. §103(a) - Obviousness

The Examiner rejected claims 50-57 under 35 U.S.C. §103(a) as allegedly obvious over Columbo (J. of Immunology) in view of Mohammadi (Science).

In response to the Examiner's rejection of claims 50-57, applicant respectfully traverses, and maintains that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims. In support of this traversal, applicant incorporates herein by reference the arguments in applicant's November 18, 2002 Amendment, March 19, 2002 Communication and August 14, 2001 Amendment. Applicant also sets forth the following remarks to underscore his position.

Again, claims 50-57 provide methods for treating or preventing cutaneous inflammation. These methods comprise administering to a subject an amount of an antibody that binds to kit protein, thereby preventing or treating cutaneous inflammation.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Here, the cited references fail to support a *prima facie* case of obviousness. Specifically, to support a *prima facie* case of obviousness, one of ordinary skill would have to have been motivated to combine the teachings of the cited references at the time of the invention. Moreover, these references would also have to provide a reasonable expectation of success.

The Examiner's combination of cited references provides no reasonable expectation of success of the claimed methods by one of ordinary skill at the time of invention. The cited references only teach *in vitro* experiments and data without providing *in vivo* data relating to using the claimed methods to prevent or treat cutaneous inflammation. Hence, the cited references do not provide any reasonable expectation that an anti-c-kit receptor ligand or antibody can be used to *successfully* treat or prevent cutaneous inflammation *in vivo* via blocking the SCF-KIT signaling pathway. This notion is further elaborated upon below.

Columbo only teaches a human recombinant c-kit receptor

ligand stem cell factor (rhSCF) and, as the Examiner concedes, its effects on the release of inflammatory mediators from human skin mast cells and peripheral blood basophils *in vitro*. Nowhere does Columbo suggest that anti-c-kit receptor ligand or antibody can be used *in vivo* to treat or prevent any disease, let alone cutaneous inflammation, via blocking the SCF-KIT signaling pathway.

Mohammadi does nothing more than disclose a new class of protein tyrosine kinase inhibitors based on an oxindole core (indolinones) and its effect on fibroblast growth factor receptor 1 (FGFR1) in NIH 3T3 cells. Although Mohammadi states that the selective inhibitors of protein tyrosine kinases have considerable therapeutic value, this statement, at most, applies strictly to indolinones, such as 3-[4-(1-formylpiperazin-4-yl)-benzylidenyl]-2-indolinone (SU4984) and 3-[(3-(2-carboxyethyl)-4-methylpyrrol-2-yl)methylene]-2-indolinone (SU5402), and their ability to inhibit the protein tyrosine kinase activity of FGFR1 *in vitro*. (Mohammadi, pages 955-956). Nowhere does Mohammadi suggest that indolinones are anti-c-kit ligands or that an anti-c-kit ligand can be used to prevent or treat any disease, let alone cutaneous inflammation, *in vivo* via blocking the SCF-KIT signaling pathway.

Applicant maintains that the combination of Columbo and Mohammadi would not have supported a reasonable expectation of success of the claimed methods by one of ordinary skill at the time of invention. Columbo and Mohammadi teach only *in vitro* experiments and data, without sharing *in vivo* data relating to the therapeutic

use of KIT protein inhibitors in relation to cutaneous inflammation. Applicant stresses that here, one cannot reasonably expect what will happen *in vivo* based on *in vitro* experiments. In support, applicant respectfully directs the Examiner to page 41, lines 5-32 of the subject application.

The Examiner asserts that one routinely bases *in vivo* methods upon *in vitro* experiments which is why *in vitro* experiments are performed, and one would have a high expectation of success in doing so.

Applicant respectfully disagrees. A high expectation of success cannot be equated with an incentive to experiment. Although *in vitro* experiments may provide an incentive to create *in vivo* models, there still remains uncertainty in successfully replicating *in vitro* data in *in vivo* models. The complexity of an *in vivo* model presents new difficulties and challenges absent *in vitro* experiments. In this application, the success observed in transgenic mice used in the direct therapeutic administration of anti c-kit antibodies on inflamed skin was not predictable based on an *in vitro* system. Such lack of predictability is based on *in vivo* variables, such as systemic adverse reactions in the subject, efficiency of anti c-kit antibody binding to KIT protein *in vivo*, and variable reactions associated with different inflamed tissue sites. In support of this position, applicant respectfully directs the Examiner to Ando, et al., "Effects of Chronic Treatment with the c-kit Ligand, Stem Cell Factor, on Immunoglobulin E-dependent Anaphylaxis in Mice", J. Clin. Invest., 92:1639-1649 (See Exhibit A

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of applicant's March 17, 2003 Preliminary Amendment) and the specification of the subject application on page 41, lines 5-32.

Accordingly, the Examiner has failed to establish the *prima facie* obviousness of claims 50-57 over the cited references.

In view of the above remarks, applicant maintains that claims 50-57 satisfy the requirements of 35 U.S.C. §103(a).

Rejection Under 35 U.S.C. §112, First Paragraph - Enablement

The Examiner rejected claims 50-57 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner asserted that the specification, while being enabling for inhibiting the KIT protein in mice by administering ACK2 monoclonal antibodies as a form of treating, does not support a method of preventing or treating cutaneous inflammation in humans with any antibody that inhibits KIT protein.

In response, applicant respectfully traverses. In support of this traversal, applicant incorporates herein by reference the arguments in the November 18, 2002 Amendment, March 19, 2002 Communication and August 14, 2001 Amendment. Applicant also sets forth the following

remarks to underscore his position.

Applicant maintains that the specification supports a method for treating cutaneous inflammation in humans. The specification contains sufficient working examples, i.e., *in vivo* experiments and data using anti-c-kit antibody on transmembrane/soluble SCF transgenic mice, for a method of preventing or treating cutaneous inflammation by inhibiting KIT protein in humans. Support is found at page 9, line 29 to page 10, line 9; page 30, line 19 to page 31, line 6; page 32, lines 8-25; and Figure 9 of the specification. In the specification, applicant has shown that the transmembrane/soluble SCF transgenic mouse model used in the studies histologically simulates human spongiotic dermatitis (a form of eczema) and that Croton Oil-treated SCF transgenic mice demonstrate the same histological responses as human postinflammatory hyperpigmentation. In Figure 8, applicant has also shown that SCF transgenic mice that have been afflicted with cutaneous inflammation, i.e., ear swelling, caused by allergic or irritant contactants can be treated with anti-c-kit antibody to decrease the swelling. By providing these working examples in the specification, applicant maintains that one skilled in the art would make and use the claimed invention to treat cutaneous inflammation on humans without undue experimentation.

Moreover, applicant maintains that the Examiner fails to meet the initial burden of showing that applicant's *in vivo* transgenic mouse model would not be expected to correlate with humans with respect to cutaneous

inflammation. According to the M.P.E.P. §2164.02,

"[s]ince the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an invariable exact correlation is not required."

Nowhere in the December 4, 2003 Office Action does the Examiner give any reason to suggest a lack of correlation between a transgenic mouse model and human regarding cutaneous inflammation. Therefore, the Examiner has failed to satisfy his initial burden under M.P.E.P. §2164.02.

The Examiner also cites *In re Wands* and provides a *Wands* analysis in support of the assertion that claims 50-57 would require undue experimentation for one skilled in the art to make and use the claimed invention.

Applicant points out that even though the Examiner has correctly recited all eight of the *Wands* factors, as articulated in that case, the Examiner merely provides short conclusory statements without articulating any reasoning or support for each statement. According to M.P.E.P. §2164.04, the Examiner must "mak[e] specific findings of fact, supported by the evidence, and then draw[] conclusions based on these findings of fact" when establishing a *prima facie* case for lack of enablement. Furthermore, specific technical reasons always require support by references. (See *Id.*). Without any reasoning

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or support for the conclusory statements found in the Examiner's *Wands* analysis, the Examiner again has failed to satisfy his initial burden under M.P.E.P. §2164.02.

The Examiner also states that the types of administration recited in Claim 57 are not taught in the specification.

Applicant respectfully disagrees and points out that amended Claim 57 is taught on page 15, lines 14-18 and page 48, lines 12-16 in the instant specification. Furthermore, applicant notes that one skilled in the art would make and use the claimed invention to treat cutaneous inflammation via the types of administration recited in amended Claim 57 on humans without undue experimentation.

In view of the above remarks, applicant maintains that claims 50-57 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Summary

Applicant maintains that the claims pending are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing

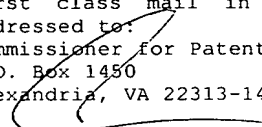
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of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicant
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

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Alan J. Morrison
Reg. No. 37,399
Date